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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/000,439	SAXON, ANDREW	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9-14,16-34 and 40-49* is/are pending in the application.

4a) Of the above claim(s) *45-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9-14,16-34 and 40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/5/07 has been entered.

2. Claims 1, 4, 9-14, 16-34, and 40-49 are pending.

3. Claims 45-49 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1, 4, 9-14, 16-34 and 40-44, drawn to an isolated fusion molecule wherein the autoantigen is myelin basic protein, and a pharmaceutical composition comprising said fusion molecule are being acted upon in this Office Action.

5. New rejections are as follow.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4, 9-14, 16-34 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated fusion molecule comprising a human IgG heavy chain constant region capable of binding to a native human IgG inhibitory receptor, directly functionally connected to a myelin basic protein or an epitope of myelin basic protein wherein the epitope consisting of the amino acid sequence of SEQ ID NO: 13, (2) The fusion molecule mentioned above wherein the human IgG heavy chain constant region sequence is the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of SEQ ID NO: 3, **does not** reasonably provide enablement for any fusion molecule as set forth in claims 1, 4, 9-14, 16-34 and 40-44 for treating autoimmune multiple sclerosis. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims are drawn to any isolate fusion molecule comprising any first polypeptide comprising at least 85% identity to any IgG heavy chain constant region connected directly or indirectly via a polypeptide linker to any second polypeptide autoantigen sequence which comprises at least 90% sequence identity to any "portion" of the amino acid sequence of myelin basic protein (MBP) that are capable of cross-linking any native IgG inhibitory receptor and any native IgE receptor through myelin specific autoantibody IgE for treating and preventing any immune disease, any immune disease such as any autoimmune disease.

The term "portion" as defined in the specification at page 29 is any portion of a polypeptide may range in size from two amino acid residues to the entire amino acid sequence minus one amino acid. The term "at least a portion" encompasses portions as well as the whole of the composition of matter.

The term "high stringent conditions" as defined in the specification at page 24 "***may be*** hybridization in 50% formamide, 6x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (PH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (100 μg/ml, 0.5% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 2x SSC (sodium chloride/sodium citrate) and 0.1% SDS at 55°C, followed by a high-stringency wash consisting of 0.2x SSC containing 0.1% SDS at 42°C.

The term "IgG inhibitory receptor" as defined in the specification at page 19 is any member of inhibitory receptor superfamily (IRS), now known or hereafter discover, that is capable of attenuating an FcER-mediated response, regardless of whether it is mediated via IgE acting through a high-affinity IgE receptor, e.g. FcεRI, or a low-affinity IgE receptor FcεRII, or by another mechanism such as an autoantibody to the FcER.

The specification does not teach how to identify other portion ranging from two amino acids to myelin basic protein that has at least 10% amino acids difference in the claimed fusion protein and yet retains the activity for the intended use such as treating and preventing autoimmune disease. There is not a single fragment from the smallest to the largest fragment of myelin basic protein fused to any IgG heavy chain constant region shows any biological effect for treating immune disease, any immune disease such as autoimmune disease.

The specification discloses only an isolated fusion molecule comprising a first polypeptide consisting of the amino acid sequence of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2, which encoded by SEQ ID NO: 1 or the amino acid sequence of SEQ ID NO: 3 fused to a full length myelin basic protein (MBP) comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, see page, 80, Example 2. The specification further discloses another fusion molecule comprising human IgG Fc fused to human IgE Fc that binds to their respective IgG or IgE receptors such as high-affinity FcεRI and low-affinity FcεRII, see pages 52-55 and 78. However, the latter part is not part of the claimed invention.

The specification does not teach how to make and use any isolated fusion protein comprising any first polypeptide sequence comprising at least 85% identity with a native human IgG heavy chain constant region capable of specific binding to native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen sequence comprising at least 90% sequence identity to any portion of the amino acid sequence of any myelin basic protein (MBP) and capable of specific binding to an IgE class immunoglobulin specific for MBP. This is because the length, structure, i.e., amino sequence as to the "portion" of the amino acid sequence of any myelin basic protein (MBP) other than SEQ ID NO: 13 has not been defined. The term "portion" could be as little as two amino acids. There is no disclosure as to which portion such as which two amino acids within the full-length sequence of MBP fused to human IgG heavy chain constant region will bind to specifically to IgE class of immunoglobulin specific for MBP. Further, given the length of the "portion" is not defined, there is insufficient guidance as to enable one of ordinary skill to determine sequence identity such as 90% of such portion for the claimed isolated fusion protein. Given the numerous fusion proteins comprising any combination of first and second polypeptide, there is a lack of *in vivo* working example showing the efficacy of such fusion molecule for treating multiple sclerosis.

With respect to myelin basic protein binding to IgE class of immunoglobulin, Barsoum et al (Med Microbiol Immunol 163: 227-232, 1977; PTO 892) teach circulating IgE is not found in-patient with multiple sclerosis. This is consistent with those of other, who used more sensitive methods (see page 230, in particular). As such, it is unclear to one of ordinary skill in the art such fusion molecule could treat multiple sclerosis by crosslinking the native IgG inhibitory receptor and IgE class receptors such as FcεRI and FcεRII without additional guidance and working examples.

With respect to fusion molecule in claims 18-21, in addition to having the problem of 90% sequence identity to a portion of the amino acid sequence of myelin basic protein mentioned above, any first polypeptide sequence comprises *an* amino acid sequence having at least 85%, 90%, 95% or 98% identity to the amino acid sequence of SEQ ID NO: 3 fused to said human IgG heavy chain are not enabled. The term "*an* amino acid sequence" could be the full-length sequence of SEQ ID NO: 3 or any portion of SEQ ID NO: 3. There is lack of guidance about which amino acids within the sequence of SEQ ID NO: 3 of the first polypeptide in the claimed fusion protein should or should not be change. Further, because the length of "portion" is not disclosed, determination of the sequence identity even using the algorithm disclosed at page 23 cannot be determined unless the length of the sequence is a fixed length.

With respect to claims 22-24, there is insufficient disclosure about the "part" of hinge of a native human IgG1 constant region, the "part" of the hinge and the "part" of the hinge, CH2 and CH3 domains without the amino acid sequence. The "part" could be as little as one amino acid. There is a lack of guidance as to which amino acid or the "part" mentioned above fused to myelin basic protein for the claimed fusion molecule other than the specific amino acid sequence that could crosslink to any member of inhibitory receptor superfamily (IRS), either now known or hereafter discover, that is capable of attenuating an FcER-mediated response.

Skolnick *et al*, PTO 1449, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

Tao et al, of record, teach even a single amino acid substitution in the CH2 domain of human IgGs from Asn-297 to His for IgG1 or Lys for IgG3 affected the structure and functional properties of the human IgGs. The resulting aglycosylated IgGs lose the ability to activate complement (C) (see page 2598, Fig 2, page 2599, col. 2, third paragraph, in particular), lost the

ability to bind FcγRI (see page 2600, col. 1, first paragraph, in particular) and shortening the serum half-life of the aglycosylated IgG3 (see abstract, in particular).

With respect to first polypeptide sequence comprises an amino acid sequence encoded by a nucleic acid hybridizing under stringent conditions to at least a portion of the complement of the IgG heavy constant region nucleotide sequence of SEQ ID NO: 1 (claim 25), there is insufficient guidance about the stringent conditions to which the nucleic acid hybridize to complement of nucleotide sequence of SEQ ID NO: 1, in addition to the structure of such oligonucleotide that hybridizes to which portion of SEQ ID NO: 1.

It is known that oligonucleotide that hybridizes to a portion of the complement of SEQ ID NO: 1 does not encode the full-length sequence of the human IgG heavy chain constant region. As such, oligonucleotide encoding such peptide has no function.

Further, the state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes a IgG heavy chain constant region. Thus the structure of the oligonucleotide that encodes the portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule is not enabled.

Finally, the specification does not adequately support the breadth of the claims comprising any and all the fusion molecule that are presented. It cannot be known whether all of the permutations and combinations of IgG heavy chain constant region and MBP portion thereof covered by the claims will be effective for the intended purpose, in this case, treating autoimmune multiple sclerosis, and that the claims are too broad because they may include inoperative species. The specification exemplify fusion molecule comprising human IgG Fc fused to myelin basic protein or the specific epitope of myelin basic protein consisting of the amino acid sequence of SEQ ID NO: 13. However, there is no disclosure of the effectiveness of such fusion protein and their combinations for treating multiple sclerosis.

Warren et al (of record, abstract) teach administering myelin basic protein fragment such as MBP35-58 to multiple sclerosis patient had no effect on the anti-MBP level. However, only administering MBP 75-95 resulted in a significant in the autoantibodies over a period of one month (see abstract, in particular).

Vanderlugt et al (J immunology 164: 670-678, 2000; PTO 892) teach the mechanism(s) underlying the initiation and progression of autoimmune disease are not well understood. A number of recent studies in both animal models of autoimmune disease and their human counterparts have shown that epitope spreading, i.e., the de novo activation of autoreactive T cells by autoepitopes released secondary to inflammatory tissue damage (see page 670, col. 1, in particular). Vanderlugt et al teach clinical relapses are associated with the development of T cell response to newly emerging epitopes on the same PLP (i.e., intramolecular epitope spreading to distinct epitope) and/or different myelin epitopes (i.e., intermolecular epitope spreading to MBP epitopes), se page 676, col. 2, in particular. The process of epitope spreading has obvious important implications for the design of antigen-specific therapies for the treatment of autoimmune disease such as multiple sclerosis since these therapies will have to identify and target endogenous self epitopes associated with chronic tissue destruction. Peptide specific therapy will have to be individualized for every patient due to the myriad of potential organ-specific autoepitopes and extensive MHC diversity (see page 677, col. 2, in particular). Vanderlugt et al conclude that because determining the specificity and hierarchical order of epitope spreading in human disease such as multiple sclerosis is not currently feasible, antigen-specific therapies for ongoing treatment autoimmune disease may require additional treatment such as induction of tolerance using whole tissue extracts, mixtures of encephalitogenic proteins/peptides or costimulatory blockade (see page 677, col. 2, in particular).

Blanas et al (of record, Science 274: 1707-1709, Dec 1996; PTO 1449) teach treating autoimmune rheumatoid arthritis and multiple sclerosis by oral administering autoantigen could lead to onset of autoimmune diabetes (see abstract, in particular).

Couzin et al, of record, teach that finding the tell tale antibodies doesn't guarantee that autoimmune diabetes sill strike (See page 1863, Science 300: 1862-65, 2003). Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document).

Davidson *et al,* PTO 1449, teach that two recent phase I clinical trial for treatment of multiple sclerosis by administering myelin basic protein peptide resulted in exacerbations of multiple sclerosis (See page 346, col. 2, in particular). In the absence of guidance and vivo working example, it is unpredictable any pharmaceutical composition comprising a myriad of fusion molecule is efficacious for treating multiple sclerosis, let alone for "preventing" autoimmune disease such as relapsing multiple sclerosis.

Since the structures of the first and second polypeptides of the claimed fusion molecule mentioned above are not enabled, it follows that any first polypeptide and any second polypeptide connected through any linker (claim 26), any linker such as polypeptide linker (claims 27-28) are not enabled. It also follows that any undisclosed fusion protein comprising at least one amino terminal ubiquitination target motif (claim 29), any proteosome proteolysis signal (claims 30-31) or any endopeptidase recognition motif (claims 32-34) are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/5/07 have been fully considered but are not found persuasive.

Applicant's position is that the sequence for the constant region of IgG was well known. The sequence for the MBP was well known, as evidenced by the specification. Thus one skilled in the art would know which amino acids could be changed and still retain function. Furthermore, claim 1 contains functional language which requires that the IgG region be capable of specific binding to a native IgG inhibitory receptor and that the MBP portion be capable of specific binding to a IgE class immunoglobulin. One skilled in the art could readily test any fusion molecule constructed to determine whether it had these functions. For the reasons set forth above, withdrawal of this portion of the rejection is requested.

The Examiner states that the term "percent" is relative and can be defined by the algorithm and parameter values set. Page 23 of the specification states that the percentage identity is determined using NCBI BLAST2 software. The parameters used for the software are provided. For these reasons, withdrawal of this portion of the rejection is requested.

In addition on page 11-12 of the Office Action, the Examiner states that the term "percent" is relative and can be defined by the algorithm and parameter values set

which using the algorithm used to compare the sequences. As indicated above, the specification provides the algorithm and the parameters on page 23. The Examiner is directed to page 23. For this reason it is NOT unpredictable which amino acids sequences will have 85% identity to the heavy chain or 90% identity to a portion of MBP.

The Examiner cites Warrant et al. as allegedly teaching the administration of myelin basic protein fragment 35-58 to multiple sclerosis patients had no effect on the anti-MBP level, whereas administration of MBP 75-95 resulted in significant autoantibodies. Allegedly the specification does not teach which portion to administer. (Pages 6-7 of the Office Action) Applicant notes that the first author's name is "Warren".

With respect to the argument that one skilled in the art could readily test any fusion molecule constructed to determine whether it had these functions, it is the examiner's position that the specification merely extends an invitation to one skilled in the art to further experimentation to come up with the structure of the claimed fusion molecule.

The specification discloses only an isolated fusion molecule comprising a first polypeptide consisting of the amino acid sequence of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2, which encoded by SEQ ID NO: 1 or the amino acid sequence of SEQ ID NO: 3 fused to a full length myelin basic protein (MBP) comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, see page, 80, Example 2.

The specification does not teach how to make and use any isolated fusion protein comprising any first polypeptide sequence comprising at least 85% identity with a native human IgG heavy chain constant region capable of specific binding to native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen sequence comprising at least 90% sequence identity to any portion of the amino acid sequence of any myelin basic protein (MBP) and capable of specific binding to an IgE class immunoglobulin specific for MBP. This is because the length, structure, i.e., amino sequence as to the "portion" of the amino acid sequence of any myelin basic protein (MBP) other than SEQ ID NO: 13 has not been defined. The term "portion" could be as little as two amino acids. There is no disclosure as to which portion such as which two amino acids within the full-length sequence of MBP fused to human IgG heavy chain constant region will bind to specifically to IgE class of immunoglobulin specific

for MBP. Further, given the length of the "portion" is not defined, there is insufficient guidance as to enable one of ordinary skill to determine sequence identity such as 90% of such portion for the claimed isolated fusion protein. Given the numerous fusion proteins comprising any combination of first and second polypeptide, there is a lack of *in vivo* working example showing the efficacy of such fusion molecule for treating multiple sclerosis.

With respect to myelin basic protein binding to IgE class of immunoglobulin, Barsoum et al (Med Microbiol Immunol 163: 227-232, 1977; PTO 892) teach circulating IgE is not found in patient with multiple sclerosis. This is consistent with those of other, who used more sensitive methods (see page 230, in particular). As such, it is unclear to one of ordinary skill in the art such fusion molecule could treat multiple sclerosis by crosslinking the native IgG inhibitory receptor and IgE class receptors such as FcεRI and FcεRII without additional guidance and working examples.

With respect to the argument of "percent identity", and that the specification provides the algorithm and the parameters on page 23, it is noted that the first polypeptide comprises a sequence that is at least 85%, 90%, 95% or 98% to any portion of SEQ ID NO: 3 (claims 17-21). The term "*an* amino acid sequence" could be the full-length sequence of SEQ ID NO: 3 or any portion of SEQ ID NO: 3. There is lack of guidance about which amino acids within the sequence of SEQ ID NO: 3 of the first polypeptide in the claimed fusion protein should or should not be change. Further, because the length of portion is not disclosed, determination of the sequence identity even using the algorithm disclosed at page 23 cannot be determined.

The argument with respect to Fc sequences highly homologous to the Fc sequences of SEQ ID NO: 3 is moot because the rejection has been moot.

With respect to Warren et al reference, the Examiner thanks Applicant for pointing out the typographical error of the first author's name; "Warren" is the correct spelling.

With respect to the argument that the specification discloses stringent hybridization conditions (Claim 25) at page 23, the term "high stringent conditions" as defined in the specification at page 24 "***may be*** hybridization in 50% formamide, 6x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (PH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (100 μg/ml, 0.5% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 2x SSC (sodium chloride/sodium citrate) and 0.1% SDS at 55°C, followed by a high-stringency wash consisting of 0.2x SSC containing 0.1% SDS at 42°C.

There is insufficient guidance about the stringent conditions to which the nucleic acid hybridize to complement of nucleotide sequence of SEQ ID NO: 1, in addition to the structure of such oligonucleotide that hybridizes to which portion of SEQ ID NO: 1.

It is known that oligonucleotide that hybridizes to a portion of the complement of SEQ ID NO: 1 does not encode the full-length sequence of the human IgG heavy chain constant region. As such, oligonucleotide encoding such peptide has no function.

Further, the state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes a IgG heavy chain constant region. Thus the structure of the oligonucleotide that encodes the portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule is not adequately described. Further, claim 25 as written is improper for an isolated fusion molecule.

With respect to the argument about in vivo working example, Applicant cited published paper Zhu et al which showed that fusion molecules comprising an IgG constant region linked to an IgE constant region successfully reduces histamine release in animals. However, the claimed fusion protein comprises an IgG constant region linked to autoantigen MBP. This paper is irrelevant to the instant claimed invention. Applicant also cited Zhu et al "A chimeric human cat-fusion protein blocks cat-induced allergy" Nature Medicine 27 March 2005, which illustrates a fusion protein molecule comprising the human IgG heavy chain constant region and an allergen. This reference teaches that a fusion molecule comprising the IgG constant region and an allergen can be successfully administered to animals and used to reduce an allergic reaction. Again, this reference is also irrelevant to the claimed fusion protein for treating autoimmune multiple sclerosis.

With respect to the argument that the appearance of IgG or other antibodies against the MBP portion of the fusion molecule would not be a problem because the purpose of the molecule is to present the MBP as an "immunogen" while any reacted IgE loaded mast cells would be suppressed by the IgG Fc portion, Barsoum et al (Med Microbiol Immunol 163: 227-232, 1977; PTO 892) teach circulating IgE is not found in patient with multiple sclerosis. This is consistent with those of other, who used more sensitive methods (see page 230, in particular). As such, it is

unclear to one of ordinary skill in the art such fusion molecule comprising IgG Fc portion fused to MBP could treat multiple sclerosis by crosslinking the native IgG inhibitory receptor and IgE class receptors such as FcεRI and FcεRII without additional guidance and working examples. Further, Vanderlugt et al (J immunology 164: 670-678, 2000; PTO 892) teach the mechanism(s) underlying the initiation and progression of autoimmune disease are not well understood. A number of recent studies in both animal models of autoimmune disease and their human counterparts have shown that epitope spreading, i.e., the de novo activation of autoreactive T cells by autoepitopes released secondary to inflammatory tissue damage (see page 670, col. 1, in particular). Vanderlugt et al teach clinical relapses are associated with the development of T cell response to newly emerging epitopes on the same PLP (i.e., intramolecular epitope spreading to distinct epitope) and/or different myelin epitopes (i.e., intermolecular epitope spreading to MBP epitopes), se page 676, col. 2, in particular. The process of epitope spreading has obvious important implications for the design of antigen-specific therapies for the treatment of autoimmune disease such as multiple sclerosis since these therapies will have to identify and target endogenous self epitopes associated with chronic tissue destruction. Peptide specific therapy will have to be individualized for every patient due to the myriad of potential organ-specific autoepitopes and extensive MHC diversity (see page 677, col. 2, in particular). Vanderlugt et al conclude that because determining the specificity and hierarchical order of epitope spreading in human disease such as multiple sclerosis is not currently feasible, antigen-specific therapies for ongoing treatment autoimmune disease may require additional treatment such as induction of tolerance using whole tissue extracts, mixtures of encephalitogenic proteins/peptides or costimulatory blockade (see page 677, col. 2, in particular). As such, it would require undue experimentation of one skilled in the art to practice the claimed invention.

8. Claims 1, 4, 9-14, 16-34 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is new matter.**

The recitation of an isolated fusion molecule comprising a first polypeptide sequence comprising at least 85% identity with a native human IgG heavy chain constant region capable of specific binding to a native IgG inhibitory receptor, directly

functionally connected to a second polypeptide autoantigen sequence comprising at least 90% sequence identity to a portion of the amino acid sequence of myelin basic protein (MBP) and **capable of specific binding to an IgE class immunoglobulin specific for MBP** in claim 1 has no support in the specification and the claims as originally filed.

The specification discloses only an isolated fusion molecule comprising a first polypeptide consisting of the amino acid sequence of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2, which encoded by SEQ ID NO: 1 or the amino acid sequence of SEQ ID NO: 3 fused to a full length myelin basic protein (MBP) comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, see page, 80, Example 2. The specification further discloses another fusion molecule comprising human IgG Fc fused to human IgE Fc that binds to their respective IgG or IgE receptors such as high-affinity FcεRI and low-affinity FcεRII, see pages 52-55 and 78. However, the latter part is not part of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The specification does not describe the chimeric human IgG1 Fc fused to autoantigen MBP or portion thereof that binds to IgE class immunoglobulin specific for MBP as now amended.

With the exception of the specific fusion molecule mentioned above, there is insufficient written description about the structure associated with function of any and all fusion molecules mentioned above comprising any autoantigen sequence comprising at least 90% sequence identity to any "portion" of the amino acid sequence of myelin basic protein. This is because the amino sequence as to the "portion" of the amino acid sequence of myelin basic protein (MBP) has not been adequately described other than the amino acid sequence of SEQ ID NO: 13. The term "portion" could be as little as two amino acids. There is no disclosure as to which portion such as which two amino acids within the full-length sequence of MBP fused to human IgG heavy chain constant region will bind to specifically to IgE class of immunoglobulin specific for MBP.

Further, given the length of the "portion is not defined, there is insufficient disclosure to enable one of ordinary skill to determine sequence identity such as 90% of such portion for the claimed isolated fusion protein.

With respect to fusion molecule in claims 18-21, in addition to having the problem of 90% sequence identity to a portion of the amino acid sequence of myelin basic protein mentioned above, the first polypeptide sequence comprises *an* amino acid sequence having at least 85%, 90%, 95% or 98% identity to the amino acid sequence of SEQ ID NO: 3 fused to said human IgG heavy chain is not adequately described. This is because the first polypeptide comprises a sequence that is at least 85%, 90%, 95% or 98% to any portion of SEQ ID NO: 3. The term "*an* amino acid sequence" could be the full-length sequence of SEQ ID NO: 3 or any portion of SEQ ID NO: 3. There is inadequate written description about which amino acids within SEQ ID NO: 3 of the first polypeptide in the claimed fusion protein should or should not be change. Since the length of portion is not defined, the sequence identity to such portion is not adequately described.

With respect to claims 22-24, there is insufficient written description about the "part" of hinge of a native human IgG1 constant region, the "part" of the hinge and the "part" of the hinge, CH2 and CH3 domains without the amino acid sequence. The "part" could be as little as one amino acid. There is a lack of written disclosure as to which amino acid or the "part" mentioned above fused to myelin basic protein for the claimed fusion molecule other than the specific amino acid sequence.

Skolnick *et al*, PTO 1449, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

With respect first polypeptide sequence comprises an amino acid sequence encoded by a nucleic acid hybridizing under stringent conditions to at least a portion of the complement of the IgG heavy constant region nucleotide sequence of SEQ ID NO: 1 (claim 25), there is insufficient written disclosure about the structure of the nucleic acid that hybridized to the complement of the SEQ ID NO: 1 in addition to the stringent conditions to which the nucleic acid hybridize to complement of nucleotide sequence of SEQ ID NO: 1, in addition to the structure of such oligonucleotide that hybridizes to which portion of SEQ ID NO: 1.

It is known that oligonucleotide that hybridizes to a portion of the complement of SEQ ID NO: 1 does not encode the full-length sequence of the human IgG heavy chain constant region. As such, oligonucleotide encoding such peptide has no function.

Further, the state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes an IgG heavy chain constant region. Thus the structure of the oligonucleotide that encodes the portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule is not adequately described. Further, claim 25 as written is improper for an isolated fusion molecule.

Finally, the specification does not adequately support the breadth of the claims comprising any and all the fusion molecule that are presented. It cannot be known whether all of the permutations and combinations of IgG heavy chain constant region and MBP portion thereof covered by the claims will be effective for the intended purpose, in this case, treating autoimmune multiple sclerosis, and that the claims are too broad because they may include inoperative species. The specification exemplify fusion molecule comprising human IgG Fc fused to myelin basic protein or the specific epitope of myelin basic protein consisting of the amino acid sequence of SEQ ID NO: 13. However, there is no disclosure of the effectiveness of such fusion protein and their combinations for treating multiple sclerosis.

Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself for the fusion molecule is required. Until the amino acid sequences of the first, and second polypeptides in the fusion protein have been described, the fusion molecule comprising the first and second polypeptide is not adequately described. Since the fusion molecule is not adequately described, it follows that any pharmaceutical composition and article of manufacture comprising any undisclosed fusion molecules are not adequately described.

Finally, the specification discloses only fusion molecule comprises a hinge-CH2-CH3 from only human IgG1 constant region consisting of SEQ ID NO: 2 fused to only myelin basic protein comprising SEQ ID NO: 12 (full length) or a peptide from myelin basic protein consisting of SEQ ID NO: 13 for treating autoimmune multiple sclerosis, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of fusion molecule to describe the genus. Thus, Applicant was not in possession of the claimed

genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments filed 7/5/07 have been fully considered but are not found persuasive. Applicant's position is that an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO:I fused to a human IgE constant region CH2-CH3-CH4 domains of SEQ ID NO:7 for inhibiting IgE mediated release of histamine is not the claimed invention. The specification describes multiple fusion molecules. For example, the Specification describes the construction of chimeric fusion molecules, see Example 2, pages 180-183. The Specification also describes fusion molecules where the first and second polypeptide sequences of the fusion molecule are connected by use of linkers (see Specification page 27, lines 4-15). Also, the fusion molecules may contain post translational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation or prenylation (as described in the Specification at page 21, line 4 - 24). The Specification describes advantageous fusion molecule variants (page 21, line 25 - page 23, line 3), where the variants have improved affinity for their respective IgG or IgE receptors (Specification, page 34, line 24 - page 35, line 25). The Specification describes fusion molecules comprising multiple copies of IgG and autoantigen (page 54, lines 18-21). Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate fusion molecule purification the fusion molecules (page 63, line 32 to page 64, line 3) are also described.

In response, the invention such as fusion protein comprising the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 2 or 3 fused to a human IgE constant region CH2-CH3-CH4 domains that binds to their respective IgG or IgE receptors is not part of the claimed invention is acknowledged.

This leaves us with the other fusion molecule. The specification discloses only an isolated fusion molecule comprising a first polypeptide consisting of the amino acid sequence of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2, which encoded by SEQ ID NO: 1 or the amino acid sequence of SEQ ID NO: 3 fused to a full length myelin basic protein

(MBP) comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting of the amino acid sequence of SEQ ID NO: 13, see page, 80, Example 2.

Adequate written description requires more than a mere statement that it is part of the invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed fusion molecule and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The amino acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

In the instant case, the specification does not describe the chimeric human IgG1 Fc fused to autoantigen MBP or portion thereof *that binds to IgE class immunoglobulin specific for MBP* as now amended.

Further, there is insufficient written description about the structure associated with function of any and all fusion molecules mentioned above comprising any autoantigen sequence comprising at least 90% sequence identity to any "portion" of the amino acid sequence of myelin

basic protein. This is because the amino sequence as to the "portion" of the amino acid sequence of myelin basic protein (MBP) has not been adequately described other than the amino acid sequence of SEQ ID NO: 13. The term "portion" could be as little as two amino acids. There is no disclosure as to which portion within the full-length sequence of MBP fused to human IgG heavy chain constant region will bind specifically to IgE class of immunoglobulin specific for MBP. Further, given the length of the "portion" is not defined, there is insufficient disclosure to enable one of ordinary skill to determine sequence identity such as 90% of such portion for the claimed isolated fusion protein.

With respect to fusion molecule in claims 18-21, in addition to having the problem of 90% sequence identity to "a portion" of the amino acid sequence of myelin basic protein mentioned above, the first polypeptide sequence comprises *an* amino acid sequence having at least 85%, 90%, 95% or 98% identity to the amino acid sequence of SEQ ID NO: 3 fused to said human IgG heavy chain is not adequately described. This is because the first polypeptide comprises a sequence that is at least 85%, 90%, 95% or 98% to any portion of SEQ ID NO: 3. The term "*an* amino acid sequence" could be the full-length sequence of SEQ ID NO: 3 or any portion of SEQ ID NO: 3. There is inadequate written description about which amino acids within SEQ ID NO: 3 of the first polypeptide in the claimed fusion protein should or should not be change. Since the length of portion is not defined, the sequence identity to such portion is not adequately described.

With respect to claims 22-24, there is insufficient written description about the "part" of hinge of a native human IgG1 constant region, the "part" of the hinge and the "part" of the hinge, CH2 and CH3 domains without the amino acid sequence. The "part" could be as little as one amino acid. There is a lack of written disclosure as to which amino acid or the "part" mentioned above fused to myelin basic protein for the claimed fusion molecule other than the specific amino acid sequence.

Skolnick *et al* teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

With respect first polypeptide sequence comprises an amino acid sequence encoded by a nucleic acid hybridizing under stringent conditions to at least a portion of the complement of the IgG heavy constant region nucleotide sequence of SEQ ID NO: 1 (claim 25), there is insufficient written disclosure about the stringent conditions to which nucleic acid hybridizes to complement

of nucleotide sequence of SEQ ID NO: 1, in addition to the structure of such oligonucleotide that hybridizes to which portion of SEQ ID NO: 1.

It is known that oligonucleotide that hybridizes to a portion of the complement of SEQ ID NO: 1 does not encode the full-length sequence of the human IgG heavy chain constant region. As such, oligonucleotide encoding such peptide has no function.

Further, the state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes an IgG heavy chain constant region. Thus the structure of the oligonucleotide that encodes the portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule is not adequately described. Further, claim 25 as written is improper for an isolated fusion molecule.

Finally, the specification does not adequately support the breadth of the claims comprising any and all the fusion molecule that are presented. It cannot be known whether all of the permutations and combinations of IgG heavy chain constant region and MBP portion thereof covered by the claims will be effective for the intended purpose, in this case, treating autoimmune multiple sclerosis, and that the claims are too broad because they may include inoperative species. The specification exemplify fusion molecule comprising human IgG Fc fused to myelin basic protein or the specific epitope of myelin basic protein consisting of the amino acid sequence of SEQ ID NO: 13. However, there is no disclosure of the effectiveness of such fusion protein and their combinations for treating multiple sclerosis.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 4, 9-14, 19, 24, and 40-41 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/01732 publication (published January 13, 2000; PTO 892).

The WO 00/01732 publication teaches an isolated fusion protein comprising a first polypeptide such as human IgG constant region capable of binding to an Fc receptor fused to a second polypeptide autoantigen such as myelin basic protein (MBP) or portion thereof (see claims 1-3 and 5 of publication, page 8, page 10, lines 15-16, page 15, line 31-33, in particular). The term "comprising" is open-ended. It expands the claimed portion of myelin basic protein to include additional amino acids at either or both ends to read on the full-length myelin basic protein. The reference human IgG heavy chain constant region inherently capable of binding to human native IgG inhibitory receptors such as low-affinity FcyRIIb IgG receptor (see page 15, lines 31-33, in particular) while the reference myelin basic protein portion of the fusion protein inherently capable of binding to IgE class immunoglobulin specific for said myelin basic protein in patient. The reference full-length myelin basic protein sequence inherently comprises at least one autoantigenic epitope. The WO 00/01732 publication further teaches a pharmaceutical composition comprising the reference fusion protein and appropriate excipients or pharmaceutically acceptable carrier or diluent (see abstract, page 19, line 28-31, page 23, line 29-31, in particular).

Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties such as IgG heavy chain constant capable of binding to a native IgG inhibitory receptor and myelin basic protein capable of binding to IgE class immunoglobulin specific MBP are inseparable. Therefore, if the prior art teaches the identical chemical structure, i.e., having the exact amino acid sequence, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Further, artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See Atlas Powder Co. V IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Claim 10 is included in this rejection because the term "comprising" is open-ended. It expands the epitope of SEQ ID NO: 13, which is residues 83-99 of myelin basic protein, to include additional amino acid residues at either ends to read on the full-length myelin basic protein. Reach-through claims 12-13 are included in this rejection because the IgE class of immunoglobulin found in patient with autoimmune multiple sclerosis inherently binds to both

IgE receptors such as high-affinity FcεRI and low-affinity FcεRII. Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/01732 publication (published January 13, 2000; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892).

The teachings of the WO 00/01732 publication have been discussed supra. The WO 00/01732 publication further teaches fusion protein comprising human IgG heavy chain constant region such as Fc fused to myelin basic protein or portion thereof is useful for treating autoimmune multiple sclerosis (see abstract, claims of the WO 00/01732 publication, in particular).

The invention in claim 10 differs from the teachings of the reference only in that the fusion protein wherein the autoantigen sequence comprises the amino acid sequence of SEQ ID NO: 13.

The '980 patent teaches autoantigen such as human myelin basic protein (MBP) and various fragments of MBP such as SEQ ID NO: 18-23, and 16 (see claims of '980 patent, in particular). The reference MBP peptide ENPVVHFFKNIVTPRTP of SEQ ID NO: 18 is 100% identical to the claimed peptide of SEQ ID NO: 13. The '980 patent teaches a pharmaceutical composition comprising protein incorporating immuno dominant epitopes of the reference

peptides and pharmaceutical acceptable carrier for administration to patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the myelin basic protein or portion thereof in the IgG heavy chain constant fusion molecule of WO 00/01732 publication for the portion of myelin basic protein (MBP) that is 100% identical to at least a portion of the amino acid sequence of myelin basic protein (MBP) as taught by the '980 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '980 patent teaches protein incorporating immuno dominant epitope of the reference peptides is useful as a pharmaceutical composition for treating patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular). The WO 00/01732 publication teaches fusion protein comprising human IgG heavy chain constant region such as Fc fused to myelin basic protein or portion thereof is useful for treating autoimmune multiple sclerosis (see abstract, claims of the WO 00/01732 publication, in particular).

14. Claims 1, 16 and 22-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/01732 publication (published January 13, 2000; PTO 892) in view of US Pat No. 5,116,964 (May 1992; PTO 892).

The teachings of the WO 00/01732 publication have been discussed supra. The WO 00/01732 publication further teaches fusion protein comprising human IgG heavy chain constant region such as Fc fused to myelin basic protein or portion thereof is useful for treating autoimmune multiple sclerosis (see abstract, claims of the WO 00/01732 publication, in particular).

The invention in claim 16 differs from the teachings of the reference only in that the fusion protein wherein the IgG is selected from the group consisting of IgG1, IgG2, IgG3, and IgG4.

The '964 patent teaches an isolated fusion molecule comprising a first polypeptide such as the constant domain of the IgG heavy chain or the Fc portion of human IgG1, IgG2, IgG3, IgG4 which obviously capable of binding to its native IgG inhibitory receptor such as FcγRIIb

IgG receptor fused to a second polypeptide autoantigen sequence such as myelin-associated glycoprotein (MAG) or a portion thereof (see abstract, col. 1, line 34, col. 7, line 45, col. 10, lines 10-15, col. 14, lines 65-67, col. 15, lines 4-17, claims 5 and 7, in particular). The '964 patent teaches the fusion protein wherein the Fc constant retain at least functionally active hinge, CH2, and CH3 domains of an immunoglobulin heavy chain (see col. 10, lines 10-25, in particular). The reference IgG heavy chain constant region in the fusion molecule has at least 98% sequence identity to the claimed human IgG Fc of SEQ ID NO: 2 (see reference SEQ ID NO: 7, in particular). The advantage of Fc improves the in vivo plasma half-life of the fusion molecule (see col. 15, lines 19-20, in particular). The '964 patent teaches a pharmaceutical composition comprising the reference fusion molecule and pharmaceutical acceptable ingredient such as calcium non-phosphate buffer and/or cofactor (see col. 31, lines 4-10, in particular). The '964 patent further teaches the fusion molecule wherein the first and second polypeptide are functionally connected through a polypeptide linkers such lysine residues, as well as other amino, amino, carboxyl, sulfhydryl, hydroxyl or other hydrophilic groups (see col. 23, lines 40-44, in particular). The '964 patent further teaches the reference fusion molecule includes a signal sequence at the N-terminus of hybrid molecule (see col. 26, lines 24-29, in particular), and a secretory leader recognized by the host cells (see col. 26, lines 32-56, in particular). The term "comprises" is open-ended. It expands the claimed CH2 and CH3 domains to include the hinge region of IgG1. Claim 25 is included in this rejection because the recitation of nucleic acid hybridizing under stringent conditions to at least a portion of the complement of the IgG heavy chain constant region of claimed human IgG Fc of SEQ ID NO: 1 would obviously include the reference human IgG Fc.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made with the expectation of success to substitute the human IgG constant region in the fusion protein comprising human Fc fused to myelin basic protein of the WO 00/01732 publication for the various constant region of human IgG such as IgG1, IgG2, IgG3 and IgG4 and then fuse the Fc region and the myelin basic protein or portion thereof either with or without a peptide linker as taught by the '964 patent.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the Fc improves the *in vivo* plasma half-life of any protein fused to Fc as taught by the' 964 patent (see col. 15, lines 19-20, in particular). The WO 00/01732 publication teaches fusion protein comprising human IgG heavy chain constant region such as Fc

fused to myelin basic protein or portion thereof is useful for treating autoimmune multiple sclerosis (see abstract, claims of the WO 00/01732 publication, in particular).

15. Claims 1 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/01732 publication (published January 13, 2000; PTO 892) in view of US Pat No 5,565,335 (of record, issued Oct 1996; PTO 892).

The combined teachings of the WO 00/01732 publication have been discussed supra. The WO 00/01732 publication further teaches fusion protein comprising human IgG heavy chain constant region such as Fc fused to myelin basic protein or portion thereof is useful for treating autoimmune multiple sclerosis (see abstract, claims of the WO 00/01732 publication, in particular).

The invention in claim 18 differs from the teachings of the reference only in that the fusion protein wherein the first polypeptide sequence comprises an amino acid sequence having at least 85% identity to the amino acid sequence of SEQ ID NO: 3 instead of any human IgG Fc as taught by the WO 00/01732 publication.

The invention in claim 19 differs from the teachings of the reference only in that the fusion protein wherein the first polypeptide sequence comprises an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 3.

The invention in claim 20 differs from the teachings of the reference only in that the fusion protein wherein the first polypeptide sequence comprises an amino acid sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 3.

The '335 patent teach various fusion molecule comprising IgG heavy chain constant region polypeptide having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3, which is at least 85%, 90%, and 95% identical to the claimed SEQ ID NO: 3 (See reference SEQ ID NO 7, in particular). The reference IgG heavy chain is fused to a second autoantigen polypeptide such as myelin associated glycoprotein (See col. 4, Detailed description, lines 18-31, in particular). The advantage of the Fc in the fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the IgG heavy chain constant region (Fc) polypeptide in the fusion molecule of the WO 00/01732 publication for the human IgG1 Fc having the amino acid

sequence that is at least 97.2 % identical the claimed SEQ ID NO: 2 as taught by the '335 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '335 patent teaches that Fc fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, in particular). The Fc improves the in vivo plasma half-life of the fusion molecule as taught by the '964 patent (see col. 15, lines 19-20, in particular). The WO 00/01732 publication teaches fusion protein comprising human IgG heavy chain constant region such as Fc fused to myelin basic protein or portion thereof is useful for treating autoimmune multiple sclerosis (see abstract, claims of the WO 00/01732 publication, in particular).

16. Claims 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/01732 publication (published January 13, 2000; PTO 892) in view of US Pat No. 5,116,964 (May 1992; PTO 892) as applied to claims 1, 16 and 22-28 mentioned above and further in view of Elias et al (of record, J Biol Chem 265(26): 15511-17, September 1990; PTO 892) and Marks et al (of record, J Cell Biol 135(2): 341-354, Oct 1996; PTO 892).

The combined teachings of the WO 00/01732 publication and the '964 patent have been discussed supra.

The claimed invention in claim 29 differs from the combined teachings of the references only in that the fusion molecule comprises at least one amino terminal ubiquitination target motif.

The claimed invention in claim 30 differs from the combined teachings of the references only in that the fusion molecule comprises at least one proteasome proteolytic signal, wherein said signal is selected from the group consisting of large hydrophobic amino acid residues, basic amino acid residues, and acidic amino acid residues.

The claimed invention in claim 31 differs from the combined teachings of the references only in that the fusion molecule comprises large hydrophobic amino acid residues, basic residues, and acid amino acid residues.

The claimed invention in claim 32 differs from the combined teachings of the references only in that the fusion molecule comprises at least one endopeptidase recognition motif.

The claimed invention in claim 33 differs from the combined teachings of the references only in that the fusion molecule comprises a plurality of endopeptidase recognition motifs.

The claimed invention in claim 34 differs from the combined teachings of the references only in that the fusion molecule comprises at least one endopeptidase recognition motif selected form the group consisting of cysteine amino acid residue.

Elias et al teach N-terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase and conjugated protein to ubiquitin targets the protein for protein degradation (See page col. 15511, col. 2, second paragraph, in particular). Elias et al teach protein with hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and lysine determines the half-life of the protein (See paragraph, bridging page 15511 and 15512, in particular).

Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to include at least one amino terminal ubiquitination target motif such as large hydrophobic amino acid residue such as leucine as taught by Elias and Marks to the fusion molecule comprising human IgG heavy chain constant region fused to myelin basic protein (MBP) or portion thereof as taught by the WO 00/01732 publication or the fusion molecule comprising human IgG heavy chain constant region from IgG1 fused to myelin basic protein (MBP) or portion thereof as taught by WO 00/01732 publication and the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Elias et al teach adding hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and/or lysine to the amino terminal of any protein would modulate the half-life of the protein (See page 1552, col. 1, in particular). Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular). It is within the purview of one ordinary skill in the art at the time the invention was made to have more than one endopeptidase recognition motifs since it is an obvious variation of the reference teachings of Mark et al.

17. Claims 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/01732 publication (published January 13, 2000; PTO 892) in view of US Pat No 5,945,294 (of record, Aug 1999, PTO 892).

The combined teachings of the WO 00/01732 publication have been discussed supra. The WO 00/01732 publication further teaches fusion protein comprising human IgG heavy chain constant region such as Fc fused to myelin basic protein or portion thereof is useful for treating autoimmune multiple sclerosis (see abstract, claims of the WO 00/01732 publication, in particular).

The claimed invention in claim 42 differs from the combined teachings of the reference only in that an article of manufacture comprising a container, a fusion molecule of claim 1 within the container, and a label or package insert on or associated with the container.

The claimed invention in claim 43 differs from the combined teachings of the reference only in that an article of manufacture comprising a container, a fusion molecule of claim 9 within the container, and a label or package insert on or associated with the container.

The claimed invention in claim 44 differs from the combined teachings of the reference only in that an article of manufacture comprising a container, a fusion molecule of claim 9 within the container, and a label or package insert on or associated with the container wherein the label or package insert comprises instructions for the treatment of an immune disease.

The '294 patent teaches diagnostic kit, which is an article of manufacture (for IgE detection using human Fc epsilon receptor (See abstract, in particular). The kit is useful for diagnosing abnormal conditions in animals that are associated with changing levels of IgE associated with allergy (See column 15, lines 19-23, in particular). A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human Fc epsilon receptor in a kit as taught by the '294 patent for the fusion molecule comprising human IgG heavy chain constant region fused to a myelin basic protein (MBP) or portion thereof as taught by the WO 00/01732 publication.

One would have been motivated, with a reasonable expectation of success to do this for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular). From the teaching of the references, it is apparent that one of

ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

18. Claims 17 and 21 are free of prior art.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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